REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As noted in the Office Action Summary, claims 1-12 and 16-31 are pending. Claims 1, 18, 22, and 23 are amended herein. Basis for the amendments may be found throughout the specification and claims as-filed, especially at page 8, line 34, page 10, line 24 and line 30, as well as claims 8, 10, and 17 as-filed. Thus, no prohibited new matter is presented herein.

Claims 2, 3, 4, 8, 9, 16, 17, 29, 30, and 31 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled by way of the present Amendment.

As claims 2-4, 8-9, 16-17, and 29-31 are canceled herein, the remaining pending claims are addressed below.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-12 and 16-31 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. The Office states that the term "predominantly containing adenoviruses" is vague and indefinite. As suggested by the Examiner, claim 1 is amended herein to recite "A method of inactivating enveloped viruses in a preparation containing recombinant adenoviruses...". Claims 18, 22, and 23 are amended to depend on claim 1. Thus, this rejection is obviated.

Claims 1-12 and 16-31 stand rejected for purportedly omitting essential positive method steps. In the interest of expediting prosecution, claim 1 is amended herein to recite the nature of the solvent (TNBP), a preferred range of solvent concentration (0.1% to 0.6%), and a preferred range of temperatures and pH (+4°C to +37°C) and (6.5 to 8.5).

However, Applicants also submit that the claimed method does not need to recite specific steps which define production and purification of adenoviruses, because such steps are not critical to the success of the claimed process.

A viral preparation meant for human use preferably combines a high degree of purity and a high degree of safety. Page 3 of the present specification states that adenovirus vectors produced by certain known preparation processes were not safe, due to the fear of potential contamination with enveloped viruses which may occur at different steps of the purification process. As stated on page 3, of the specification:

> The sources of contamination are many throughout the method which leads to the preparation of the viruses of interest. In addition, to accidental contamination, the cell lines used to propagate the viruses of interest may comprise, integrated into their chromosomes, a number of retroviral genomes (proviruses). These may be activated in response to certain culture conditions, generating infectious enveloped viruses. Furthermore, the culture media frequently contain serum of animal origin which is a major source of enveloped viruses. Furthermore, the operators, environment and the equipment for multiple uses may also contribute to the contamination.

It is well known that contamination by enveloped viruses may result in cancers, hepatitis, AIDS, and other conditions. Thus, the claimed inactivation method introduces an additional degree of safety

Further, as specifically discussed on page 19, lines 26-30, of the specification, the skilled artisan would understand that the presently claimed inactivation method

fits into a process for preparing recombinant adenoviruses. When read in light of the specification, the inactivation method of the invention could be introduced at various stage of the preparation process, for example, as indicated on page 20, lines 5-9 of the specification (after the recovery of the viruses from a producer cell line, or after the removal of cellular debris).

Therefore, steps which define production and purification of adenoviruses are not critical to the present inactivation method. In further support, Applicants note that in the Office Action [restriction requirement] mailed on July 30, 2002, the Office considered the fact that the recitation of additional steps such as virus recovery from a producer cell line, removal of cellular debris, degradation of residual nucleic acids and recovery of the virus by some type of filtration process would result in a method of preparing an adenovirus preparation as claimed in original claims 13 and 14. Thus, Applicants submit that such steps are not necessary.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-12 and 16-31 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification purportedly fails to provide sufficient enablement. The Office states that the disclosure is not broad enough to encompass the claim language. Applicants respectfully traverse.

The Office cites to specific embodiments recited in the specification, such as the inactivation protocol involving recombinant adenoviral preparations and specific inactivation steps involving treatment with 0.3% tri-n-butyl phosphate (TNBP), 1% TWEEN 80, and benzonase. However, Applicants submit that the reaction conditions set forth in the working examples of the present application (*i.e.*, TNBP

concentration of 0.3% at pH of 8.5 and a temperature of 4°C or room temperature) are merely the optimal conditions at least for the adenovirus preparations described therein (*see* Example 1, page 38, lines 9-23, Examples 3 and 5).

However, Applicants point out that these conditions may vary within the presently claimed ranges without significantly altering the viral yield. Given the guidance provided in the specification, the skilled artisan can practice the claimed method to remove enveloped viruses contained in an adenovirus preparation with nothing more than routine experimentation. In further support, Applicants cite to additional studies performed by the inventors in order to study the effect of the concentration of TNBP (0.1% to 0.6%) and pH (pH5 to 8.5) upon the infectious activity of the adenovirus preparation. These studies show that the infectious activity of the adenovirus is maintained within the whole of the concentration range tested for TNBP (0.1% to 0.6%) and at a pH varying from 6 to 8.5. Thus, these comparative studies show that a number of parameters are flexible.

With regard to the reaction temperature, Applicants submit that adenoviruses tolerate a wide range of temperatures. Adenoviruses can be stocked at refrigeration temperature (+4°C) and are routinely propagated at 37°C, without any reduction of the viral titers.

In conclusion, the method of inactivating enveloped viruses contained in an adenovirus preparation as presently claimed are enabled. Applicants request that this rejection be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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